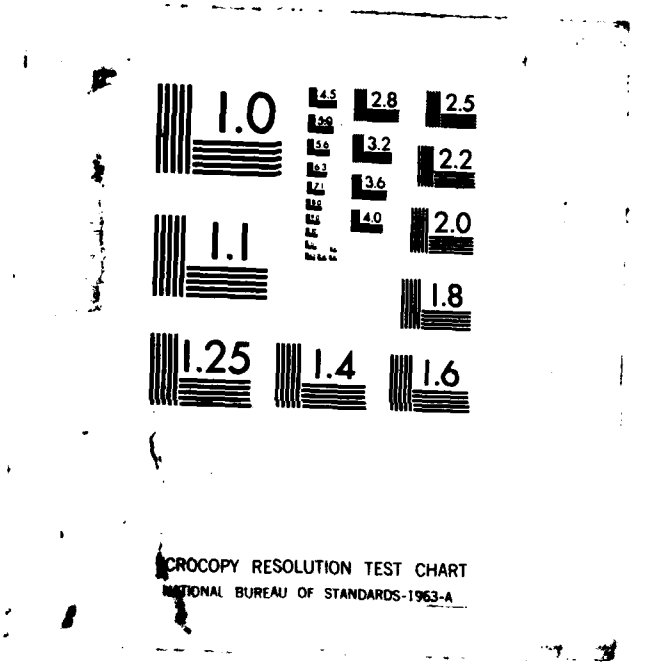
AD-A174 113 GLOMERULAR DYNAMIC STUDIES OF THE PATHOGENESIS OF ACUTE 1/1
RENAL FAILURE(U) VIRGINIA COMMONWEALTH UNIV RICHMOND
D E OKEN 30 JUN 84 DAMD17-83-C-3144

UNCLASSIFIED F/G 6/5 NL


1.0
1.1
1.25
1.4
1.6
1.8
2.0
2.2
2.5
2.8
3.2
3.6
4.0
4.5
5.0
5.6
6.3
7.1
CROCOPY RESOLUTION TEST CHART
NATIONAL BUREAU OF STANDARDS-1963-A

SECURI

AD-A174 113 ENTATION PAGE

Form Approved
OMB No 0704-0188
Exp. Date Jun 30, 1986

1a. REPORT SECURITY CLASSIFICATION	1b. RESTRICTIVE MARKINGS
2a. SECURITY CLASSIFICATION AUTHORITY	3. DISTRIBUTION/AVAILABILITY OF REPORT: Distribution unlimited; Approved for public release
2b. DECLASSIFICATION/DOWNGRADING SCHEDULE	
4. PERFORMING ORGANIZATION REPORT NUMBER(S): DAMD17-83-C-3144	5. MONITORING ORGANIZATION REPORT NUMBER(S): 62772A-3S162772A874.AB159
6a. NAME OF PERFORMING ORGANIZATION: Medical College of Virginia Virginia Commonwealth Univ. / 6b. OFFICE SYMBOL (If applicable)	7a. NAME OF MONITORING ORGANIZATION: US Army Medical Research and Development Command
6c. ADDRESS (City, State, and ZIP Code): 1101 East Marshall Street Box 160 - MCV Station Richmond, Virginia 23298-0001	7b. ADDRESS (City, State, and ZIP Code): Fort Detrick Frederick, Maryland 21701-5012
8a. NAME OF FUNDING/SPONSORING ORGANIZATION: US Army Medical Research and Development Command / 8b. OFFICE SYMBOL (If applicable)	9. PROCUREMENT INSTRUMENT IDENTIFICATION NUMBER
8c. ADDRESS (City, State, and ZIP Code): Fort Detrick Frederick, Maryland 21701-5012	10. SOURCE OF FUNDING NUMBERS

PROGRAM ELEMENT NO.	PROJECT NO.	TASK NO.	WORK UNIT ACCESSION NO.
62772A	3S1-62772A874	AB	159

11. TITLE (Include Security Classification): Glomerular Dynamic Studies of the Pathogenesis of Acute Renal Failure - (Unclassified)

12. PERSONAL AUTHOR(S): Donald E. Oken, M.D.

13a. TYPE OF REPORT	13b. TIME COVERED	14. DATE OF REPORT (Year, Month, Day)	15. PAGE COUNT
FINAL	FROM 06/15/83 TO 06/14/84	June 30, 1984	6

16. SUPPLEMENTARY NOTATION

17. COSATI CODES			18. SUBJECT TERMS (Continue on reverse if necessary and identify by block number)
FIELD	GROUP	SUB-GROUP	Acute renal failure, glomerular dynamics, glomerular filtration, renovascular resistances.
20	06		
06	05		

19. ABSTRACT (Continue on reverse if necessary and identify by block number)

The aberrations in glomerular dynamic parameters attendant upon mercury induced acute renal failure have been evaluated in this study. As judged by several criteria, glomerular filtration is virtually totally abolished 16-26 hours after mercury injection. The majority of nephrons are totally collapsed and proximal tubule pressures are decidedly subnormal. The fall in glomerular filtration rate is not attributable to tubular obstruction but is directly related to alterations in pre- and postglomerular vascular resistances. The R_A/R_E ratio is markedly increased and probably represents preglomerular vasoconstriction concomitantly with an element of postglomerular vascular relaxation. Studies designed to determine the relative importance of this vascular change in these two vascular segments are continuing.

The present results are in preparation for publication.

DTIC ELECTE NOV 18 1986 S A

20. DISTRIBUTION/AVAILABILITY OF ABSTRACT	21. ABSTRACT SECURITY CLASSIFICATION
☒ UNCLASSIFIED/UNLIMITED ☐ SAME AS RPT. ☐ DTIC USERS	UNCLASSIFIED

22a. NAME OF RESPONSIBLE INDIVIDUAL	22b. TELEPHONE (Include Area Code)	22c. OFFICE SYMBOL
Mrs. Virginia M. Miller	301/663-7325	SGRD-RMI-S

DD FORM 1473, 84 MAR — 83 APR edition may be used until exhausted. All other editions are obsolete. SECURITY CLASSIFICATION OF THIS PAGE

DTIC FILE COPY

Block 9. Procurement Instrument Identification Number: For a contractor grantee report, enter the complete contract or grant number(s) under which the work was accomplished. Leave this block blank for in-house reports.

Block 10. Source of Funding (Program Element, Project, Task Area, and Work Unit Number(s): These four data elements relate to the DoD budget structure and provide program and/or administrative identification of the source of support for the work being carried on. Enter the program element, project, task area, work unit accession number, or their equivalents which identify the principal source of funding for the work required. These codes may be obtained from the applicable DoD forms such as the DD Form 1498 (Research and Technology Work Unit Summary) or from the fund citation of the funding instrument. If this information is not available to the authoring activity, these blocks should be filled in by the responsible DoD Official designated in Block 22. If the report is funded from multiple sources, identify only the Program Element and the Project, Task Area, and Work Unit Numbers of the principal contributor.

Block 11. Title: Enter the title in Block 11 in initial capital letters exactly as it appears on the report. Titles on all classified reports, whether classified or unclassified, must be immediately followed by the security classification of the title enclosed in parentheses. A report with a classified title should be provided with an unclassified version if it is possible to do so without changing the meaning or obscuring the contents of the report. Use specific, meaningful words that describe the content of the report so that when the title is machine-indexed, the words will contribute useful retrieval terms.

If the report is in a foreign language and the title is given in both English and a foreign language, list the foreign language title first, followed by the English title enclosed in parentheses. If part of the text is in English, list the English title first followed by the foreign language title enclosed in parentheses. If the title is given in more than one foreign language, use a title that reflects the language of the text. If both the text and titles are in a foreign language, the title should be translated, if possible, unless the title is also the name of a foreign periodical. Transliterations of often used foreign alphabets (see Appendix A of MIL-STD-847B) are available from DTIC in document AD-A080 800.

Block 12. Personal Author(s): Give the complete name(s) of the author(s) in this order: last name, first name, and middle name. In addition, list the affiliation of the authors if it differs from that of the performing organization.

List all authors. If the document is a compilation of papers, it may be more useful to list the authors with the titles of their papers as a contents note in the abstract in Block 19. If appropriate, the names of editors and compilers may be entered in this block.

Block 13a. Type of Report: Indicate whether the report is summary, final, annual, progress, interim, etc.

Block 13b. Time Covered: Enter the inclusive dates (year, month, day) of the period covered, such as the life of a contract in a final contractor report.

Block 14. Date of Report: Enter the year, month, and day, or the year and the month the report was issued as shown on the cover.

Block 15. Page Count: Enter the total number of pages in the report that contain information, including cover, preface, table of contents, distribution lists, partial pages, etc. A chart in the body of the report is counted even if it is unnumbered.

Block 16. Supplementary Notation: Enter useful information about the report in hand, such as: "Prepared in cooperation with...," "Translation at (or by)...," "Symposium...," If there are report numbers for the report which are not noted elsewhere on the form (such as internal series numbers or participating organization report numbers) enter in this block.

Block 17. COSATI Codes: This block provides the subject coverage of the report for announcement and distribution purposes. The categories are to be taken from the "COSATI Subject Category List" (DoD Modified), Oct 65, AD-624 000. A copy is available on request to any organization generating reports for DoD. At least one entry is required as follows:

Field - to indicate subject coverage of report

Group - to indicate greater subject specificity of information in the report.

Sub-Group - if specificity greater than that shown by Group is required, use further designation as the numbers after the period (.) in the Group breakdown. Use only the designation provided by AD-624 000.

Example: The subject "Solid Rocket Motors" is Field 21, Group 08, Subgroup 2 (page 32, AD-624 000).

Block 18. Subject Terms: These may be descriptors, keywords, posting terms, identifiers, open-ended terms, subject headings, acronyms, code words, or any words or phrases that identify the principal subjects covered in the report, and that conform to standard terminology and are exact enough to be used as subject index entries. Certain acronyms or "buzz words" may be used if they are recognized by specialists in the field and have a potential for becoming accepted terms. "Laser" and "Reverse Osmosis" were once such terms.

If possible, this set of terms should be selected so that the terms individually and as a group will remain UNCLASSIFIED without losing meaning. However, priority must be given to specifying proper subject terms rather than making the set of terms appear "UNCLASSIFIED." Each term on classified reports must be immediately followed by its security classification, enclosed in parentheses.

For reference on standard terminology the "DTIC Retrieval and Indexing Terminology" DRIT-1979, AD-A068 500, and the DoD "Thesaurus of Engineering and Scientific Terms (TEST) 1968, AD-672 000, may be useful.

Block 19. Abstract: The abstract should be a pithy, brief (preferably not to exceed 300 words), factual summary of the most significant information contained in the report. However, since the abstract may be machine-searched, all specific and meaningful words and phrases which express the subject content of the report should be included, even if the word limit is exceeded.

If possible, the abstract of a classified report should be unclassified and consist of publicly releasable information (Unlimited), but in no instance should the report content description be sacrificed for the security classification.

NOTE: **An unclassified abstract describing a classified document may appear separately from the document in an unclassified context e.g., in DTIC announcement or bibliographic products. This must be considered in the preparation and marking of unclassified abstracts.**

For further information on preparing abstracts, employing scientific symbols, verbalizing, etc., see paragraphs 2.1(n) and 2.3(b) in MIL-STD-847B.

Block 20. Distribution / Availability of Abstract: This block must be completed for all reports. Check the applicable statement: "unclassified / unlimited," "same as report," or, if the report is available to DTIC registered users "DTIC users."

Block 21. Abstract Security Classification: To ensure proper safeguarding of information, this block must be completed for all reports to designate the classification level of the entire abstract. For CLASSIFIED abstracts, each paragraph must be preceded by its security classification code in parentheses.

Block 22a,b,c. Name, Telephone and Office Symbol of Responsible Individual: Give name, telephone number, and office symbol of DoD person responsible for the accuracy of the completion of this form.

GPO : 1986 O - 499-863

INSTRUCTIONS FOR PREPARATION OF REPORT DOCUMENTATION PAGE

GENERAL INFORMATION

The accuracy and completeness of all information provided in the DD Form 1473, especially classification and distribution limitation markings, are the responsibility of the authoring or monitoring DoD activity.

Because the data input on this form will be what others will retrieve from DTIC's bibliographic data base or may determine how the document can be accessed by future users, care should be taken to have the form completed by knowledgeable personnel. For better communication and to facilitate more complete and accurate input from the originators of the form to those processing the data, space has been provided in Block 22 for the name, telephone number, and office symbol of the DoD person responsible for the input cited on the form.

All information on the DD Form 1473 should be typed.

Only information appearing on or in the report, or applying specifically to the report in hand, should be reported. If there is any doubt, the block should be left blank.

Some of the information on the forms (e.g., title, abstract) will be machine indexed. The terminology used should describe the content of the report or identify it as precisely as possible for future identification and retrieval.

NOTE: **Unclassified abstracts and titles describing classified documents may appear separately from the documents in an unclassified context, e.g., in DTIC announcement bulletins and bibliographies. This must be considered in the preparation and marking of unclassified abstracts and titles.**

The Defense Technical Information Center (DTIC) is ready to offer assistance to anyone who needs and requests it. Call Data Base Input Division, Autovon 284-7044 or Commercial (202) 274-7044.

SECURITY CLASSIFICATION OF THE FORM

In accordance with DoD 5200.1-R, Information Security Program Regulation, Chapter IV Section 2, paragraph 4-200, classification markings are to be stamped, printed, or written at the top and bottom of the form in capital letters that are larger than those used in the text of the document. See also DoD 5220.22-M, Industrial Security Manual for Safeguarding Classified Information, Section II, paragraph 11a(2). This form should be unclassified, if possible.

SPECIFIC BLOCKS

Block 1a. Report Security Classification: Designate the highest security classification of the report. (See DoD 5220.1-R, Chapters I, IV, VII, XI, Appendix A.)

Block 1b. Restricted Marking: Enter the restricted marking or warning notice of the report (e.g., CNWDI, RD, NATO).

Block 2a. Security Classification Authority: Enter the commonly used markings in accordance with DoD 5200.1-R, Chapter IV, Section 4, paragraph 4-400 and 4-402. Indicate classification authority.

Block 2b. Declassification / Downgrading Schedule: Indicate specific date or event for declassification or the notation, "Originating Agency Determination Required" or "OADR." Also insert (when applicable) downgrade to _____ on _____ (e.g., Downgrade to Confidential on 6 July 1983). (See also DoD 5220.22-M, Industrial Security Manual for Safeguarding Classified Information, Appendix II.)

NOTE: **Entry must be made in Blocks 2a and 2b except when the original report is unclassified and has never been upgraded.**

Block 3. Distribution/Availability Statement of Report: Insert the statement as it appears on the report. If a limited distribution statement is used, the reason must be one of those given by DoD Directive 5200.20, Distribution Statements on Technical Documents, as supplemented by the 18 OCT 1983 SECDEF Memo, "Control of Unclassified Technology with Military Application." The Distribution Statement should provide for the broadest distribution possible within limits of security and controlling office limitations.

Block 4. Performing Organization Report Number(s): Enter the unique alphanumeric report number(s) assigned by the organization originating or generating the report from its research and whose name appears in Block 6. These numbers should be in accordance with ANSI STD 239.23-74, "American National Standard Technical Report Number." If the Performing Organization is also the Monitoring Agency, enter the report number in Block 4.

Block 5. Monitoring Organization Report Number(s): Enter the unique alphanumeric report number(s) assigned by the Monitoring Agency. This should be a number assigned by a DoD or other government agency and should be in accordance with ANSI STD 239.23-74. If the Monitoring Agency is the same as the Performing Organization, enter the report number in Block 4 and leave Block 5 blank.

Block 6a. Name of Performing Organization: For in-house reports, enter the name of the performing activity. For reports prepared under contract or grant, enter the contractor or the grantee who generated the report and identify the appropriate corporate division, school, laboratory, etc., of the author.

Block 6b. Office Symbol: Enter the office symbol of the Performing Organization.

Block 6c. Address: Enter the address of the Performing Organization. List city, state, and ZIP code.

Block 7a. Name of Monitoring Organization: This is the agency responsible for administering or monitoring a project, contract, or grant. If the monitor is also the Performing Organization, leave Block 7a. blank. In the case of joint sponsorship, the Monitoring Organization is determined by advance agreement. It can be either an office, a group, or a committee representing more than one activity, service, or agency.

Block 7b. Address: Enter the address of the Monitoring Organization. Include city, state, and ZIP code.

Block 8a. Name of Funding/Sponsoring Organization: Enter the full official name of the organization under whose immediate funding the document was generated, whether the work was done in-house or by contract. If the Monitoring Organization is the same as the Funding Organization, leave 8a blank.

Block 8b. Office Symbol: Enter the office symbol of the Funding/Sponsoring Organization.

Block 8c Address: Enter the address of the Funding/ Sponsoring Organization. Include city, state and ZIP code.

AD _____

Glomerular Dynamic Studies of the Pathogenesis of Acute Renal Failure

Final Comprehensive Report

Donald E. Oken, M.D.

June 30, 1984

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701-5012

Contract No. DAMD17-83-C-3144

Virginia Commonwealth University
Richmond, Virginia 23298

DOD Distribution Statement

Approved for public release; distribution unlimited

The findings in this report are not to be construed as an official Department of the Army position unless so designated by other authorized documents.

SUMMARY

The aberrations in glomerular dynamic parameters attendant upon mercury induced acute renal failure have been evaluated in this study. As judged by several criteria, glomerular filtration is virtually totally abolished 16-26 hours after mercury injection. The majority of nephrons are totally collapsed and proximal tubule pressures are decidedly subnormal. The fall in glomerular filtration rate is not attributable to tubular obstruction but is directly related to alterations in pre- and postglomerular vascular resistances. The R_A/R_E ratio is markedly increased and probably represents preglomerular vasoconstriction concomitantly with an element of postglomerular vascular relaxation. Studies designed to determine the relative importance of this vascular change in these two vascular segments are continuing.

The present results are in preparation for publication.

INTRODUCTION

This proposal was developed to examine the abnormalities in glomerular dynamics responsible for the development of failed filtration in experimental models of acute renal failure. As given in the initial proposal, the work was estimated to occupy a three-year period. The report concerns the research accomplished in the first year of support.

Although there have been many studies of glomerular dynamics in various physiologic and pathologic settings in the past, we could find no reports in which the various methodologies have been validated or the effect of internephron heterogeneity established. The degree of internephron and interanimal heterogeneity of each of the parameters measured in studies of glomerular dynamics in normal rats was examined here as a necessary requisite to subsequent studies in acute renal failure. In this aspect of the study, nephron glomerular filtration rate (SNGFR), glomerular capillary (P_g) Bowman's space (P_{BS}) and star vessel (P_{star}) hydrostatic pressures were measured along with nephron filtration fraction (SNFF) in quintuplicate in eleven normal Munich-Wistar rats. No correlation was found between the mean SNGFR values of the 11 animals and P_g, P_{star} or P_{BS} ($p > 0.2$ or higher). P_g for the individual rats did not correlate with P_{BS} or P_{star} ($p > 0.4$). The intraanimal coefficients of variation (SD/mean) for SNFF and SNGFR averaged 0.188±SEM 0.013 and 0.119±0.010, respectively ($n = 11$). P_g, P_{BS} and P_{star} showed rather less intra-animal variability, their coefficients of variation averaging 0.069±SEM 0.007, 0.087±0.008 and 0.091±0.006, respectively. The interanimal coefficients of variation for these same parameters were: P_g 0.072; P_{BS}, 0.051; P_{star}, 0.054; SNGFR, 0.072; and SNFF 0.111, values which, with the exception of P_g, are significantly lower than the corresponding intra-animal coefficients of variation ($p < 0.001$). The intra- and interanimal coefficients of variation in both P_g, COP_E were not significantly different ($p > 0.2$).

As found in the earlier study of Arendshorst and Gottschalk, a large residual net filtration pressure left the animals in the present series far from filtration pressure equilibrium. The mean ultrafiltration coefficient was found to be notably lower than that in many (e.g. 2) but not all reports in the literature. Under this circumstance, glomerular plasma flow, rendering decreased plasma flow only a potential secondary role in the genesis of filtration failure, changes in the ultrafiltration coefficient and/or individual vascular resistances thus being essential to the development of near total cessation of filtration experimental renal failure (see below). Standard statistical equations were adapted to permit estimates of variances of the derived parameters of glomerular dynamics taking into account both the intra- and interanimal variances of the constituent measured parameters, information essential to the proper interpretation of glomerular dynamic alterations in the developmental phases of acute renal failure. A manuscript

describing these experiments will be submitted to Kidney International.

STUDIES OF EXPERIMENTAL ACUTE RENAL FAILURE

This study relates to the glomerular dynamic changes to be found in acute renal failure produced by subcutaneous injection of nephrotoxic doses (9 mg/kg B.W.) of mercuric chloride. Studies were performed 16-26 hours after mercury injection. The animals were anesthetized with sodium pentobarbital and the kidney was exposed for micropuncture in standard fashion. Cannulae were placed for arterial pressure measurement and the intravenous infusion of fluids prior to placement of a tracheostomy tube. The left kidney was isolated and embedded in agarose to minimize respiratory and pulsatile movement. As viewed through the dissecting microscope, the kidney surface was surveyed to determine the degree of tubular filling, the proportion totally collapsed tubules, the size of "star" vessels and the rapidity of blood flow in peritubular capillaries. The presence of tubular flow was determined qualitatively from the rate of progression of small oil droplets injected into proximal tubules. Nephron filtration rate was determined directly by quantitative fluid collection from the glomerulo-tubular junction. (SNGFR estimated in this way obviated the possibility that SNGFR values might be underestimated by tubular inulin leakage if measured in the customary fashion.) Nephron filtration fraction was estimated from the concentration of ^{125}I albumin in star vessel and systemic blood according to the equation SNFF = $(1-I^{*}_{A}/I^{*}_{E})$. Pressures in glomerular capillaries, "star" vessels, and in Bowman's space were measured by the Landis and servo-null methods in different series of rats.

Nephron filtration rate, estimated by direct quantitative collection of fluid at the glomerulo-tubular junction, was unmeasurably low in all but three of 79 nephrons studied in 23 rats. Nephron filtration fraction derived from 57 star vessels of 17 rats was 0-102$\pm$SEM 0.05, a value significantly greater than zero ($p < 0.01$) but less than control (0.29 ± 0.03, $N = 55$).

Lissamine green injected iv as a bolus normally appears with fresh filtrate in Bowman's space and is seen to flow rapidly down the tubule. Injected in this fashion into rats with mercuric chloride induced acute renal failure, very faint staining of filtrate was seen in some glomeruli but this coloration disappeared within 5-20 seconds without ever passing the glomerulo-tubular junction into proximal tubules. Lissamine green did not appear at all in the majority of glomeruli. Injected in isotonic saline directly into Bowman's space until fluid just appeared in the most proximal segment of the proximal tubule, lissamine green became progressively more pale over a 2-4 minute period. In no instance, however, was it propelled down the tubule by the formation of new filtrate. After luminal occlusion with heavy mineral oil, fluid (i.e. fresh filtrate)

could be obtained from the glomerulo-tubular junction (GTJ) in measurable quantities (i.e. 5 nl or more) in only one of 44 attempts in 13 rats over a 3-5 minute period. (Normal fluid delivery rate at the GTJ is 28±SEM 1.0 nl/min). This value is indistinguishable from the SNGFR of 29.7±0.6 nl/min) measured with ^{14}C inulin by conventional micropuncture methods ($p > 0.4$), $N = 55$). This, as manifest by failure of lissamine green to appear in Bowman's space in reasonable concentration after iv injection, failure of lissamine green injected directly into Bowman's space to enter the glomerulo-tubular junction and the absence of fluid entry into the tubular system as documented by direct collections from the glomerulo-tubular junction, glomerular filtration was virtually absent in virtually all surface nephrons. Further evidence for the near total cessation of filtration was obtained by injecting small droplets of low viscosity, stained silicone oil into 103 randomly selected proximal tubular segments of 23 animals. Normally, this injectate flows briskly along the proximal tubule and disappears from view almost instantaneously. In every instance, droplets injected into proximal tubules of rats with mercury poisoning remained totally stationary for up to 30 minutes with no tendency to forward propulsion.

Bowman's space and proximal tubule pressures averaged 9.7±1.4 mmHg (control 11.6±SEM 0.18 mmHg). These values were obtained from the small minority of nephrons that contained sufficient fluid to permit pressure measurements. Pressure could not be measured accurately in the remaining nephrons but, since fluid could be injected into the proximal tubule of collapsed nephrons at hydrostatic pressures of 5-9 mmHg, elevated intratubular pressure cannot be incriminated as a major contributor to filtration failure in this model of ARF. With a mean glomerular capillary pressure of 25.6±2.1 mmHg (control 49.2±3.6 mmHg) and a mean colloid osmotic pressure in systemic arterial plasma of 11.4±1.6 mmHg (versus control 15.6±1.4 mmHg), $p < 0.001$),. mean net afferent filtration pressure was thus 4.5 mmHg, a figure far lower than the value of 21.6 mmHg found in control rats ($p < 0.001$). Mean star vessel pressure was 8.4±1.1 mmHg (control 12.6±0.9 mmHg). Estimates of pre- (R_A and postglomerular (R_E) require values for glomerular blood flow which cannot be determined with conventional techniques in the absence of glomerular filtration. Afferent and efferent blood flows, however, are equal when glomerular filtration is absent. Accordingly, when expressed as a ratio, R_A/R_E, the relative magnitudes of R_A and R_E can be assessed from the equation: $R_A/R_E = (MAP - P_g)/(P_g - P_{star})$. In the present study, the R_A/R_E ratio of mercury injected rats was found to be 4.5, a figure considerably higher than the control value of 1.8. Very marked heterogeneity in individual values was found, however, necessitating the extension of this study to include more data. In ongoing studies, moreover, renal cortical blood flow is being measured in each rat employing implanted cortical platinum electrodes and the hydrogen washout technique to facilitate interpretation of the R_A/R_E ratios by network modeling.

END

12-86

DTIC